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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,982	04/25/2001	Scott L. Diamond	PENN0754	3650

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/763,982	Diamond et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 28, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *8* is/are allowed.

6) ☒ Claim(s) *1-7 and 9-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Apr 25, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/03 has been entered.

Applicant's amendment submitted 1/31/03 has been entered as Paper No. 13.

Claims 1-13 are pending and are under consideration in this Office Action.

Rejections Withdrawn

Applicant's amendments overcome the rejections under 35 USC 102.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1, 2, 4, 5, 7, and 9-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4, 5, 7, and 9-13 are drawn to the genus of non-classical nuclear localization signals (NLSs) that do not interact with importin alpha or importin beta. The claims recite no structural limitations at all, and the genus is defined solely on the basis of its functional characteristics.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The central issue in this analysis is whether Applicant has disclosed a number of species which is representative of the claimed genus.The genus of non-classical NLSs is of indeterminant size, however it is fair to assume that these sequences have alleles in the species from which they were isolated, as well as homologs in other species. The general knowledge in the art concerning

alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art, the structure of one does not provide guidance as to the structure of others. Thus the structure of the alleles which could reasonably be expected to occur in nature is highly unpredictable. As such, the structure of homologous or orthologous peptides from other species would be even more unpredictable. Further, it is possible that other as yet undiscovered non-classical NLSs exist which are not homologous to M9 or KNS.

The specification discloses three non-classical NLSs by name: M9 of hnRNPA1, KNS of hnRNP K, and HNS of HuR. Only two of these are described by structure, i.e. M9 is contained in SEQ ID NOS: 1 and 3, and KNS is contained in SEQ ID NO:4. An alignment between these two sequences was carried out using BLASTP. No significant similarity was detected. See attached results. The specification fails to establish what are the structural characteristics that define a non-classical NLS, and further fails to provide any known or disclosed correlation between structure and function that could be considered to be an adequate description of relevant identifying characteristics. The sequences of allelic, homologous, or orthologous NLSs would be impossible to predict, in view of the failure of the specification to provide guidance as to the structural features required to provide the claimed function, and in view of the apparent variability in the genus as evidence by the lack of similarity between the disclosed non-classical NLS sequences. As such, based on the disclosure of only two non-classical NLSs, one of skill in the

art could not conclude that Applicant was in possession of the claimed genus at the time of the invention.

Enablement

Claims 1, 2, 4, 5, 7, and 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising nuclear localization peptides comprising SEQ ID NOS: 3 or 4, wherein the peptides do not interact with importin alpha or importin beta, does not reasonably provide enablement for the broader genus of all nuclear localization peptides that do not interact with importin alpha or importin beta. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. .

As noted above, the claims are drawn to the genus of non-classical nuclear localization signals (NLSs) that do not interact with importin alpha or importin beta.

The specification teaches the sequences of only two such peptides although it is reasonable to assume that others exist, such as alleles, homologs, orthologs, and possibly unrelated sequences which are not yet known.

A sequence alignment between the two disclosed sequences (SEQ ID NOS: 3 and 4) shows no similarity between them.

The specification fails to provide any guidance as to what are the structural features that provide the claimed functional features, i.e. nuclear localization without interaction with importin alpha or beta. Similarly, the prior art of record fails to provide any guidance in this regard.

Due to the total lack of similarity between the two disclosed peptides, and the lack of guidance in the specification and prior art regarding the structure required for the claimed activity, one of skill in the art would have to perform empirical experimentation in order to make non-classical NLSs other than SEQ ID NOS: 3 and 4. However, the prior art teaches the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as

> mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the prior art indicate that the relationship between protein structure and function is unpredictable. In view of the fact that the specification and prior art provide no guidance as to what nucleic acid sequences are required for nuclear localization in the absence of importin alpha and beta interaction, nor any guidance as to what mechanisms provide such transport, one of skill in the art would have no scientific laws or models to resort to in the process of empirically determining what sequences fulfill the functions required by the claims, and would have to perform undue experimentation in order to make this determination. Accordingly, the specification adequately enables on those compositions and methods that require the use of NLSs comprising SEQ ID NOS: 3 and 4.

The specification also fails to enable the full scope of claims 4-6, 11 for the following reasons. These claims are drawn to methods of delivering a selected molecule to the nucleus of a eukaryotic cell, wherein the method requires contacting the cells with the molecule and with a nuclear targeting peptide containing a non-classical nuclear localization signal. The claims require no physical linkage between the molecule and the targeting peptide. The specification teaches means for associating molecules with targeting peptides, and methods of using the resulting complexes to deliver the associated molecules to cell nuclei. However, the specification fails to teach how to deliver molecules to the nucleus of cells that have been, or will be, contacted with a

nuclear targeting peptide that is not in some direct or indirect fashion attached to the molecule. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the failure to teach how to achieve delivery of selected molecules to a cell nucleus without attaching the molecules in some way to a nuclear targeting peptide. Accordingly the claims are enabled only for the scope of the invention in which the targeting peptide is in some way attached to the selected molecule.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because its metes and bounds are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Jost et al (Nucl. Acids Res. (1997) 25(15): 3131-3134).

Jost teaches cells stably transfected with a plasmid. See abstract. Jost is considered to anticipate the claims because the claim does not require the presence in the cell of a complex comprising a scaffold-nuclear targeting peptide conjugate. Rather the claim is a product-by process claim that is anticipated by any stably transfected cell comprising a plasmid. This is because the recited scaffold-nuclear targeting peptide conjugate, as described in the specification, is composed of biodegradable materials that would not be expected to persist in a cell line that is maintained in continuous culture.

Thus Jost anticipates the claim.

Response to Arguments

Applicant's arguments filed 1/31/03 have been fully considered but they do not apply to the new grounds of rejection set forth above.

Conclusion

Claim 8 is allowable. Claims 1-7, and 9-12 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.